Exhibit F

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23.3.1. (d)

(d) Tests for chiral new drug substances: Where a new drug substance is predominantly one enantiomer, the opposite enantiomer is excluded from the qualification and identification thresholds given in the ICH guidances on ``Q3A Impurities in New Drug Substances'' and ``Q3B Impurities in New Drug Products'' because of practical difficulties in quantifying it at those levels. However, that impurity in the chiral new drug substance and the resulting new drug product(s) should otherwise be treated according to the principles established in those guidances.

Decision Tree #5 summarizes when and if chiral identity tests, impurity tests, and assays may be needed for both new drug substances and new drug products, according to the following concepts:

Drug Substance: Impurities. For chiral drug substances that are developed as a single enantiomer, control of the other enantiomer should be considered in the same manner as for other impurities. However, technical limitations may preclude the same limits of quantification or qualification from being applied. Assurance of control also could be given by appropriate testing of a starting material or intermediate, with suitable justification.

Assay. An enantioselective determination of the drug substance should be part of the specification. It is considered acceptable for this to be achieved either through use of a chiral assay procedure or by the combination of an achiral assay together with appropriate

methods of controlling the enantiomeric impurity.

Identity. For a drug substance developed as a single enantiomer, the identity test(s) should be capable of distinguishing both enantiomers and the racemic mixture. For a racemic drug substance, there are generally two situations where a stereospecific identity test is appropriate for release/acceptance testing: (1) Where there is a significant possibility that the enantiomer might be substituted for the racemate, or (2) when there is evidence that preferential crystallization may lead to unintentional production of a nonracemic mixture.

Drug Product: Degradation products. Control of the other enantiomer in a drug product is considered necessary unless racemization has been shown to be insignificant during manufacture of the dosage form and on storage.

Assay. An achiral assay may be sufficient where racemization has been shown to be insignificant during manufacture of the dosage form and on storage. Otherwise a chiral assay should be used. Alternatively, the combination of an achiral assay plus a validated

[[Page 83047]]

procedure to control the presence of the opposite enantiomer may be used.

Identity. A stereospecific identity test is not generally needed in the drug product release specification. When racemization is insignificant during manufacture of the dosage form and on storage, stereospecific identity testing is more appropriately addressed as part

of the drug substance specification. When racemization in the dosage form is a concern, chiral assay or enantiomeric impurity testing of the drug product will serve to verify identity.